

Annex A: Highlights of the “Biotechnology Revolution”: 1953–present*

- 1953** *Nature* magazine published James Watson’s and Francis Crick’s manuscript which described the double helix structure of DNA. The **discovery of the structure of DNA** resulted in an explosion of research in molecular biology and genetics, paving the way for the “biotechnology revolution.”
- 1955** Seymour Benzer at Purdue University devised an experimental setup to map mutations within a short genetic region of a particular bacterial virus. Over a five-year period, Benzer mapped recombinations of genetic material that distinguished mutational changes that had taken place at adjacent base pairs.
- 1956** Heinz Fraenkel-Conrat took apart and reassembled the tobacco mosaic virus, demonstrating “self assembly.”
- 1957** Francis Crick and George Gamov worked out the “**central dogma**,” explaining how DNA functions to make protein. Their “sequence hypothesis” posited that the DNA sequence specifies the amino acid sequence in a protein. They also suggested that genetic information flows only in one direction, from DNA to messenger RNA to protein, the central concept of the central dogma.
- 1957** Matthew Meselson and Frank Stahl demonstrated the replication mechanism of DNA.
- 1958** Coenbergen discovered and isolated DNA polymerase, which became the first enzyme used to make DNA in a test tube.
- 1958** The National Seed Storage Laboratory (NSSI) was opened in Fort Collins, Colorado, becoming the first long-term seed storage facility in the world.
- 1959** Francois Jacob and Jacques Monod established the existence of genetic regulation—mappable control functions located on the chromosome in the DNA sequence—which they named the repressor and operon. They also demonstrated the existence of proteins that have dual specificities.
- 1959** The steps in protein biosynthesis were delineated.
- 1959** Systemic fungicides were developed.
- 1961** Marshall Nirenberg built a strand of mRNA comprised only of the base uracil. This strand is called “poly-u,” and by examining it Nirenberg discovered that UUU is the codon for phenylalanine. This was the first step in cracking the genetic code, which Nirenberg and colleagues succeeded in doing within five years.
- 1965** Scientists noticed that genes conveying antibiotic resistance in bacteria are often carried on small, supernumerary chromosomes called plasmids. This observation led to the classification of the plasmids.
- 1965** Harris and Watkins successfully fused mouse and human cells.
- 1966** The **genetic code was “cracked.”** Marshall Nirenberg, Heinrich Mathaei, and Severo Ochoa demonstrated that a sequence of three nucleotide bases (a codon) determines each of 20 amino acids.
- 1967** Arthur Kornberg conducted a study using one strand of natural viral DNA to assemble 5,300 nucleotide building blocks. Kornberg’s Stanford group then synthesized infectious viral DNA.
- 1967** Mary Weiss and Howard Green took a crucial step in human gene mapping with the publication of a technique for using human cells and mouse cells grown together in one culture. This was called **somatic-cell hybridization**.
- 1969** Leonard Herzenberg, a geneticist at Stanford, developed the fluorescence-activated cell sorter, which can identify up to 5,000 closely related animal cells.

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- 1970** Peter Duesberg and Peter Vogt, virologists at UCSF, discovered the first oncogene in a virus. This SRC gene has since been implicated in many human cancers.
- 1970** Howard Temin and David Baltimore, working independently, first isolated “**reverse transcriptase**” a restriction enzyme that cuts DNA molecules at specific sites. Their work described how viral RNA that infects a host bacteria uses this enzyme to integrate its message into the host’s DNA. This discovery allowed scientists to create clones and observe their function.
- 1970** Torbjorn Caspersson, L. Zech, and other colleagues in Sweden, published the first method for staining human or other mammalian chromosomes in such a way that banding patterns appear.
- 1972** The **Biological Weapons Convention** was signed. The purpose of this agreement was to prohibit the development, testing, and stockpiling of biological weapons. The treaty allows research for defensive purposes, such as to develop antidotes to biological weapons.
- 1972** Immunologist Hugh McDevitt, in an article in *Science*, reported observing genes that control immune responses to foreign substances. His observations suggested predictable, inherited susceptibility to some diseases.
- 1972** Paul Berg isolated and employed a restriction enzyme to cut DNA. Berg used ligase to paste two DNA strands together to form a hybrid circular molecule. This was **the first recombinant DNA molecule**.
- 1972** The first successful DNA cloning experiments were performed in California.
- 1972** In a letter to *Science*, Stanford biochemist Paul Berg and others called for the National Institutes of Health to enact guidelines for DNA splicing. Their letter recommended that scientists stop doing certain types of recombinant DNA experiments until questions of safety could be addressed. This letter was provoked by experiments planned by Berg, which had drawn vocal concern from the scientific community. Their concerns eventually led to the 1975 Asilomar Conference.
- 1973** Scientists for the first time successfully transferred deoxyribonucleic acid (DNA) from one life form into another. Stanley Cohen and Annie Chang of Stanford University and Herbert Boyer of UCSF “spliced” sections of viral DNA and bacterial DNA with the same restriction enzyme, creating a plasmid with dual antibiotic resistance. They then spliced this recombinant DNA molecule into the DNA of a bacteria, thereby producing **the first recombinant DNA organism**.
- 1973** Bruce Ames, a biochemist at UC Berkeley, developed a test to identify chemicals that damage DNA. The Ames Test becomes a widely used method to identify carcinogenic substances.
- 1973** The first human-gene mapping conference took place. The conference was inspired primarily by the rapid development in mapping by somatic-cell hybridization.
- 1974** The Proceedings of the National Academy of Sciences published a paper by Stanford geneticist Stanley Cohen and UCSF biochemist Herbert Boyer in which they demonstrated the expression of a foreign gene implanted in bacteria by recombinant DNA methods. Cohen and Boyer showed that DNA can be cut with restriction enzymes and reproduced by inserting the recombinant DNA into *Escherichia coli*.
- 1975** A moratorium on recombinant DNA experiments was called for at an international meeting at Asilomar, California, where scientists urged the government to adopt guidelines regulating recombinant DNA experimentation. The scientists insisted on the development of “safe” bacteria and plasmids that could not escape from the laboratory.
- 1975** Kohler and Milstein fused cells together to produce **monoclonal antibodies**.
- 1976** Herbert Boyer and Robert Swanson founded Genentech, Inc., a biotechnology company dedicated to developing and marketing products based on recombinant DNA technology.
- 1976** J. Michael Bishop and Harold Varmus, virologists at UCSF, showed that oncogenes appear on animal chromosomes, and alterations in their structure or expression can result in cancerous growth.

- 1976 The NIH released the first guidelines for recombinant DNA experimentation. The guidelines restricted many categories of experiments.
- 1977 Genentech, Inc., reported the production of the first human protein manufactured in a bacteria: somatostatin, a human growth hormone-releasing inhibitory factor. **For the first time, a synthetic, recombinant gene was used to clone a protein. Many consider this to be the advent of the Age of Biotechnology.**
- 1977 Sixteen bills were introduced in Congress to regulate recombinant DNA research. The bills called for the development of bacteria and plasmids that could be prevented from escaping from the laboratory environment. None of the bills passed.
- 1977 Bill Rutter and Howard Goodman isolated the gene for rat insulin.
- 1977 Walter Gilbert and Allan Maxam at Harvard University devised a method for sequencing DNA using chemicals rather than enzymes.
- 1978 Genentech, Inc. and The City of Hope National Medical Center announced the successful laboratory production of human insulin using recombinant DNA technology.
- 1978 Harvard researchers used genetic engineering techniques to produce rat insulin.
- 1978 Stanford University scientists successfully transplanted a mammalian gene.
- 1978 Studies by David Botstein and others found that when a restrictive enzyme is applied to DNA from different individuals, the resulting sets of fragments sometimes differ markedly from one person to the next. Such variations in DNA are called **restriction fragment length polymorphisms**, or RFLPs, and they are extremely useful in genetic studies.
- 1979 William J. Rutter's lab at UCSF cloned a coat protein of the virus that causes hepatitis B.
- 1979 John Baxter reported cloning the gene for human growth hormone.
- 1980 The U.S. Supreme Court ruled in the Chakrabarty case that genetically altered life forms can be patented. This ruling opened up enormous possibilities for commercially exploiting genetic engineering, which until that point had rested solely on the ability of companies to protect trade secrets.
- 1980 Kary Mullis and others at Cetus Corporation in Berkeley, California, invented a technique for multiplying DNA sequences in vitro by, the polymerase chain reaction (PCR). PCR has been called the most revolutionary new technique in molecular biology in the 1980s. Cetus patented the process, and in the summer of 1991 sold the patent to Hoffman-La Roche, Inc. for \$300 million.
- 1981 Genentech, Inc. cloned interferon gamma.
- 1981 Bill Rutter and Pablo Valenzuela published a report in *Nature* on a yeast expression system to produce the hepatitis B surface antigen.
- 1981 Scientists at Ohio University produced the first transgenic animals by transferring genes from other animals into mice.
- 1981 Mary Harper and two colleagues mapped the gene for insulin. That year, mapping by *in situ* hybridization became a standard method.
- 1981 - 1982 Congressman Al Gore held a series of hearings on the relationship between academia and commercialization in the arena of biomedical research. He focused on the effect that the potential for huge profits from intellectual property and patent rights could have on the research environment at universities. Jonathan King, a professor at MIT speaking at the Gore hearings, reminded the biotech industry that "the most important long-term goal of biomedical research is to discover the causes of disease in order to prevent disease."
- 1982 Genentech, Inc. received approval from the Food and Drug Administration to market genetically engineered human insulin.

- 1982 Applied Biosystems, Inc. introduced the first commercial gas phase protein sequencer, dramatically reducing the amount of protein sample needed for sequencing.
- 1982 Lindow requested government permission to test genetically engineered bacteria to control frost damage to potatoes and strawberries.
- 1982 Michael Smith at the University of British Columbia, Vancouver, developed a **procedure for making precise amino acid changes anywhere in a protein.**
- 1982 Richard Goldstein and Richard Novick called for the prohibition of the use of RNA technologies in the development of biological weapons.
- 1983 Syntex Corporation received FDA approval for a monoclonal antibody-based diagnostic test for *Chlamydia trachomatis*.
- 1983 Stanford Research Institute International filed for a patent for an *E. coli* expression vector.
- 1983 Jay Levy's lab at UCSF isolated the AIDS virus (human immunodeficiency virus, HIV) at almost the same moment it was isolated at the Pasteur Institute in Paris and at the NIH.
- 1983 U.S. patents were granted to companies genetically engineering plants.
- 1983 Marvin Carruthers at the University of Colorado devised a method to construct fragments of DNA of predetermined sequence from five to about 75 base pairs long. He and Leroy Hood at the California Institute of Technology invented instruments that could make such fragments automatically.
- 1984 Cal Bio scientists described in *Nature* the isolation of a gene for anaritide acetate, which helps to regulate blood pressure and control salt and water excretion.
- 1984 Stanford University received a product patent for prokaryote DNA.
- 1984 Chiron Corp. announced the first cloning and sequencing of the entire human immunodeficiency virus (HIV) genome.
- 1984 Charles Cantor and David Schwartz developed pulsed-field gel electrophoresis.
- 1985 Axel Ullrich reported the sequencing of the human insulin receptor in *Nature*. Bill Rutter's UCSF team described the sequencing in *Cell* two months later.
- 1985 Cal Bio cloned the gene that encodes human lung surfactant protein, a major step toward reducing a premature birth complication.
- 1985 *Science* reported Cetus Corporation's GeneAmp **polymerase chain reaction (PCR) technology**, which could generate billions of copies of a targeted gene sequence in only hours.
- 1985 Genetically engineered plants resistant to insects, viruses, and bacteria were field tested for the first time.
- 1985 The NIH approved guidelines for performing experiments in gene therapy on humans.
- 1985 Genetic Sciences (AGS) surreptitiously performed the first deliberate release experiment, injecting genetically engineered microbes into trees growing on the company's roof, while waiting for approval from the EPA to conduct a different deliberate release experiment involving strawberry plants.
- 1986 UC Berkeley chemist Peter Schultz described how to combine antibodies and enzymes (creating "abzymes") to create pharmaceuticals.
- 1986 A regiment of scientists and technicians at Caltech and Applied Biosystems, Inc., invented the automated DNA fluorescence sequencer.
- 1986 The FDA granted a license for the first recombinant vaccine (for hepatitis) to Chiron Corp.
- 1986 The EPA approved the release of the first genetically engineered crop, gene-altered tobacco plants.

- 1987 Genentech received FDA approval to market rt-PA (genetically engineered tissue plasminogen activator) to treat heart attacks.
- 1987 Calgene, Inc. received a patent for the tomato polygalacturonase DNA sequence, used to produce an antisense RNA sequence that can extend the shelf-life of fruit.
- 1987 Advanced Genetic Sciences, Inc. conducted a field trial of a recombinant organism, a frost inhibitor, on a Contra Costa County strawberry patch.
- 1987 Maynard Olson and colleagues at Washington University invented “yeast artificial chromosomes,” or YACs, expression vectors for large proteins.
- 1988 Philip Leder and Timothy Stewart, molecular geneticists at Harvard, introduced the “Harvard Mouse”—a line of genetically engineered laboratory mice. They were the first to win a patent for a mammal in the U.S.
- 1988 SyStemix Inc. received a patent for the SCIDHU Mouse, an immune-deficient mouse with a reconstituted human immune system. The mouse was engineered for AIDS research.
- 1988 Genencor International, Inc. received a patent for a process to make bleach-resistant protease enzymes to use in detergents.
- 1989 UC Davis scientists developed a recombinant vaccine against the deadly rinderpest virus, which had wiped out millions of cattle in developing countries.
- 1990 UCSF and Stanford University were issued their 100th recombinant DNA patent license. By the end of fiscal 1991, both campuses had earned \$40 million from the patent.
- 1990 The first successful field trial of genetically engineered cotton plants was conducted by Calgene Inc. The plants had been engineered to withstand use of the herbicide Bromoxynil.
- 1990 The FDA licensed Chiron’s hepatitis C antibody test to help ensure the purity of blood bank products.
- 1990 Michael Fromm, molecular biologist at the Plant Gene Expression Center, reported the stable transformation of corn using a high-speed gene gun.
- 1990 Mary Claire King, epidemiologist at UC-Berkeley, reported the discovery of the gene linked to breast cancer in families with a high degree of incidence before age 45.
- 1990 GenPharm International, Inc. created the first transgenic dairy cow. The cow was used to produce human milk proteins for infant formula.
- 1990 A four-year-old girl suffering from ADA deficiency, an inherited disorder that destroys the immune system, became the **first human recipient of gene therapy**. The therapy appeared to work, but set off a fury of discussion of ethics both in academia and in the media.
- 1990 The **Human Genome Project**, the international effort to map all of the genes in the human body, was launched. Estimated cost: \$13 billion.
- 1991 The celebrated reference work “Mendelian Inheritance in Man,” was made available through an on-line computer network. The catalogue lists some 5,600 genes known or thought on good evidence to be inherited in Mendelian patterns.